Papers and Originals

Assessment of British Gammaglobulin in Preventing Infectious Hepatitis

A Report to the Director of the Public Health Laboratory Service*

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Summary: A series of 87 controlled trials of the effectiveness of British gammaglobulin in preventing infectious hepatitis in schools and other institutions showed that gammaglobulin is very effective in these circumstances. No protection was given for the first two weeks after injection, probably because it was given during the incubation period of the hepatitis.

The risks of developing hepatitis in contacts was found to vary greatly. In day schools there was usually little tendency for the disease to spread among the population, but the pupils in closest contact were at greater risk. In mental hospitals and children's homes, on the other hand, the tendency for the disease to spread was more pronounced.

Introduction

Gammaglobulin (human normal immunoglobulin) prepared in the United States has been shown to prevent the clinical manifestations of infectious hepatitis (Ward and Krugman, 1962). A similar effect from material obtained from donors in other countries cannot be assumed. In the United Kingdom persons with a history of jaundice are not accepted as blood donors, and this selection might affect the antibody content of the British product. The efficacy of British gammaglobulin has now been assessed by field trials. These trials have been made in many areas of the United Kingdom and co-ordinated centrally; the findings are reported below.

Apart from its protective efficacy the usefulness of gammaglobulin depends in practice on the magnitude of the risk to contacts, which may vary in different situations. This risk has accordingly been examined by surveys. In these surveys all contacts were left uninoculated.

General Plan

The investigation began in March 1966 after pilot trials had been made in a few areas. This report includes the findings up to the end of February 1968.

Medical officers of health and physicians in charge of institutions in many areas of the United Kingdom reported to the Epidemiological Research Laboratory any case of infectious hepatitis which came to their notice in a school or other institution. The protocol of the trial, with sufficient record cards and gammaglobulin, was then sent to the medical officer or other physician. One group of contacts allocated by an effective random method was given gammaglobulin; the remaining contacts, the control group, were not given gammaglobulin. Both groups were observed and the incidence of infectious hepatitis was recorded.

The surveys were made in institutions in which a valid trial was not possible, usually because of administrative difficulties. In these surveys gammaglobulin was not given to any contact and the incidence of infectious hepatitis was recorded.

Methods

Co-ordination

The trial was co-ordinated and the findings were analysed by the staff of the Epidemiological Research Laboratory. The procedures and records were standardized throughout the investigation. Arrangements were made locally to obtain parental consent if required, to allocate the contacts to the inoculated or control group, to give the gammaglobulin, and to complete the appropriate records.

Entry, Allocation, and Follow-up

No upper or lower limit was set to the number of contacts invited to participate in any single school or institution. However, not all contacts were invited when their number was so large as to cause difficulties in completing records and giving gammaglobulin. This limited intake was almost always confined to schools in which those in closest contact with a known case—for example, classmates—were given priority. Consent—parental if required—was obtained for all contacts invited to take part. When consent had been obtained the contact was considered to be in the trial and was allocated to the appropriate group. Contacts born on an odd date of any month were allocated to receive gammaglobulin; those born on an even date were allocated to the control group. Those allocated to receive gammaglobulin but who were not inoculated because of absence or for any other reason were classed as defaulters. The defaulters, the great majority of whom were day-school pupils, were also followed up and appear in the analysis as a separate group. A record was also kept of those contacts who refused to participate.

For all contacts—irrespective of whether they had been allocated to the inoculated or the control group—the date of entry to the trial was the day on which the gammaglobulin was given at the institution. From that date all cases of infectious hepatitis occurring in the institution were considered as having developed after the start of the trial. For each case a standard record of the main clinical and laboratory findings was completed by the local physician concerned, whose diagnosis was accepted for the purposes of the trial. In each institution the follow-up ended six months after the date of occurrence of the last case of infectious hepatitis.

* The investigation was made under the auspices of the Research Group Advisory Council of the Society of Medical Officers of Health and the Scottish Home and Health Department. A very large number of medical officers of health and physicians in charge of institutions took part in the combined investigation, and personnel in various Public Health Laboratories also participated. Mrs. G. V. Smith, of the Epidemiological Research Laboratory, undertook the administration and compiled the data. Mr. J. Pope advised on the statistical analysis. The report was written by Dr. T. M. Pollock and Dr. D. Reid.

Similar procedures were used in the surveys except that, as stated above, no contacts were inoculated. The number and ages of the persons in the institution at the beginning and end of the survey were recorded. Brief clinical details and the dates of onset of each case of infectious hepatitis were entered on a standard record. As with the trials, the period of observation ended six months after the date of the occurrence of the last case of infectious hepatitis.

Trials Not Included in Main Analysis

The findings for each trial were included in the main analysis only if the procedures had been correctly followed during the entire investigation. In some instances the findings were unacceptable as a basis for a valid assessment. This was usually because the allocation to the inoculated or the control group was made first and parental consent sought only for the former. In these circumstances there was clearly some likelihood that the inoculated and control groups might not be similar. The findings of these trials and of those with other imperfections—a total of 36—have been analysed separately.

Gammaglobulin

Each batch of gammaglobulin was prepared at the Blood Products Laboratory, Lister Institute of Preventive Medicine, Elstree, from citrated plasma pooled from not less than 1,000 blood donations from normal healthy adults resident in England and Wales. Of the nine batches used, seven were prepared by fractionation with ether by the method of Kekwick and Mackay (1954), one was prepared by fractionation with ethanol by the method of Kistler and Nitschmann (1962), and one consisted of four parts ethanol fractionated and one part ether-fractionated gammaglobulin. The solution used clinically contained 15 g. of protein per 100 ml. and 1 : 10,000 thiomersal, a 250-mg. dose being contained in 1.7 ml.

The gammaglobulin was given by intramuscular injection; children under 10 years of age received 250 mg. and those of 10 years or more 500 mg.

Results

Number and Types of Institutions and Duration of Follow-up

In the 87 trials included in this analysis the plan of the investigation was closely followed. Most were in day schools: the total number of contacts in all institutions was 4,232 (Table I). The duration of observation in most trials was seven to nine months. In two trials the period of observation was more than 12 months.

TABLE I.—*Contacts According to Type of Institution*

Type of Institution	No. of Each Type	No. of Contacts
Day school	68	3,312
Boarding school	6	201
Children's home	3	98
Hospital (general)	1	24
Hospital (mental)	4	404
Day nursery	3	140
Approved school	2	53
Total	87	4,232

Similarity of Groups

If all the trials are taken into account a total of 2,050 contacts were inoculated and there were 2,053 controls. One hundred and twenty-nine contacts were allocated to the inoculated group but did not receive gammaglobulin and were classed as defaulters (Table II). During the follow-up some participants in both groups left the schools and institutions and were lost to observation. Each group was followed up with similar intensity. The proportion lost from the inoculated and control groups was the same—12%; the average period of observation was almost identical. As might be expected, the proportion of defaulters lost to observation was greater, though the average duration of the follow-up was similar to that of the other groups. The trials included contacts from infancy to adult life but most were between 5 and 14 years of age. The proportion of inoculated and controls in each age group was similar (Table II).

TABLE II.—*Age of Contacts and Duration of Follow-up According to Group*

Ages (Years)	Inoculated	Control	Defaulted
0–4	121 (5·9%)	123 (6%)	14 (10·8%)
5–9	1,221 (59·5%)	1,221 (59·4%)	71 (55·0%)
10–14	431 (21·0%)	462 (22·5%)	24 (18·6%)
15–19	79 (3·8%)	100 (4·9%)	4 (3·1%)
20+	198 (9·7%)	147 (7·2%)	16 (12·4%)
Total	2,050	2,053	129
Leaving	12%	12%	21%
Average duration (months of follow-up)	8·0	7·9	7·1

Incidence of Infectious Hepatitis in Trials

For the first two weeks after the date on which gammaglobulin was given to the inoculated group the number of contacts who developed infectious hepatitis was almost the same in each group—12 and 14 respectively (Table III). Thereafter six cases occurred in the inoculated group and 46 in the control group. A comparison of the rates in each group is shown in Table IV. Only seven patients did not have manifest jaundice, but since all seven were in the control group they have been excluded from the table to make the assessment of protection as objective as possible. The assessment shown in Table IV is based, therefore, on the relative incidence of infectious hepatitis with jaundice in both the inoculated and the control groups.

TABLE III.—*Infectious Hepatitis in Each Group According to Weeks After Start of Trial*

Group	No. of Cases Occurring after Start of Trial—Weeks											
	<1	1–	2–	3–	4–	5–	6–	7–	8+	<2	≥2	All
Inoculated	5	7	2	0	2	0	0	1	1	12	6	18
Control	6	8	5	7	8	4	4	5	13	14	46	60

TABLE IV.—*Cases of Infectious Hepatitis with Jaundice and Efficacy of Gammaglobulin (a) During Entire Period of Follow-up and (b) Excluding Cases During the First Two Weeks After Start of Trial**

Group	No. of Contacts	Cases during Entire Period			Excluding Cases during First 2 Weeks		
		Cases	Rate per 100	Protective Efficacy	Cases	Rate per 100	Protective Efficacy
Inoculated	2,050	18	0·9	65·3%	6	0·3	84·2%
Control	2,053	53 (7)	2·6		40 (6)	1·9	

* Cases of infectious hepatitis without jaundice are shown in parentheses and are not included in the assessment of protective efficacy (see text).

The rates per 100 of infectious hepatitis with jaundice were 0.9 and 2.6 for the entire period of observation. If the cases which occurred during the first two weeks are excluded the rates are 0.3 and 1.9, a protective efficacy of 84.2%.

The difference between the inoculated and the control group both for the entire period of observation and also when the first two weeks are excluded attains statistical significance at the 1% level.

When the seven patients in the control group with hepatitis without jaundice are included the corresponding rates are 0.9 and 2.9 per 100 for the entire period of observation and 0.3 and 2.2 when the cases during the first two weeks are excluded; for the latter period the protective efficacy is 87%.

Cases were less frequent among inoculated than among control contacts in all age groups (Table V).

TABLE V.—*Age of Cases According to Group*

Group	Ages in Years					
	0–4	5–9	10–14	15–19	20+	Total
Inoculated ..	1	9	4	2	2	18
Control ..	8	31	8	10	3	60

One case occurred among the 129 defaulters, a rate of 0.8 per 100. This rate was smaller than the rate in the control group because most of the defaulters came from day schools, where the risk to contacts was less than in other institutions.

A total of 1,062 persons refused to participate. Almost all were schoolchildren whose parents did not give written consent. Of the parents who refused, 34 did so because the child had had a previous attack of infectious hepatitis. There were 11 cases among those who refused, a rate of 1.0 per 100.

Diagnosis

All cases of infectious hepatitis which occurred among inoculated contacts and 53 of the 60 cases among the controls had manifest jaundice.

The physician in charge of each case was asked to record his impression of the severity of the disease. His assessment took into account all aspects of the case, and as judged by this the disease tended to be milder in inoculated persons. When the duration of jaundice and period in bed are compared there seems to be little difference between the groups (Table VI).

TABLE VI.—*Severity of Infectious Hepatitis in the 18 Inoculated and 60 Control Patients*

Group	Duration of Jaundice (Weeks)			
	Nil or <1	1–2	>2	Not Stated
Inoculated ..	5 (28%)	11 (61%)	2 (11%)	—
Control ..	17 (28%)	32 (53%)	9 (15%)	2 (3%)
	Period in Bed (Weeks)			
	Nil or <1	1–2	>2	Not Stated
Inoculated ..	5 (28%)	9 (50%)	4 (22%)	—
Control ..	24 (40%)	28 (47%)	8 (13%)	—
	Physician's Assessment of Severity			
	Mild	Moderate	Severe	Not Stated
Inoculated ..	14 (78%)	2 (11%)	1 (6%)	1 (6%)
Control ..	34 (57%)	19 (32%)	5 (8%)	2 (3%)

Trials Not Included in Main Analysis

There were 728 inoculated and 646 uninoculated contacts in the 36 trials not included in the above analysis because the trials were conducted imperfectly. The relative incidence of infectious hepatitis in these imperfect trials follows the same trend as that in the valid investigations. During the whole period of observation there were 14 cases in the inoculated group and 31 in the control group—rates of 1.9 and 4.8 per 100. If the first two weeks after inoculation are excluded the number of cases was six in the inoculated group and 19 in the control group—rates of 0.8 and 2.9 per 100.

Incidence in Uninoculated Contacts

Surveys were made in 115 institutions—almost all of which were day schools—and in these gammaglobulin was not given to any contact. In 75 institutions (65% of the total) there was a single case only, and there was no spread of manifest disease to contacts despite the absence of gammaglobulin. In only two institutions were there more than six cases; in one of these nine occurred and in the other 10 (Table VII).

TABLE VII.—*Results of 115 Surveys Showing the Number of Cases of Infectious Hepatitis*

No. of Cases	Surveys	
	No.	%
1	75	65
2	14	12
3	11	10
4	15	13

The rate per 100 cases of infectious hepatitis among the total number of persons in each type of institution is shown in Table VIII. The rate in schools for normal children is small. In the few institutions of other types which include only a rather small number of contacts the rate is much greater than in schools.

TABLE VIII.—*Incidence of Infectious Hepatitis in Surveys According to Type of Institution**

Type of Institution	No. of Surveys	No. of Contacts	Cases of Infectious Hepatitis	Rate per 100
Day school	107	34,550	194	0·6
Boarding school ..	1	1,208	4	0·3
Children's home ..	2	38	6	15·8
Detention centre ..	1	110	6	5·5
Nursery	2	89	5	5·6
Boarding school E.S.N.†	2	157	4	2·5

* No surveys were made in mental hospitals.
† For the educationally subnormal.

The infectious hepatitis rates in the schools included in the surveys are based on the *total* number of pupils in each school and not only on those considered to be close contacts of the cases. An indication of the increased risk to close contacts can be obtained from the incidence among the untreated control group in the schools in which the trials took place. (It will be remembered that because the number of pupils in most schools was large only close contacts were usually invited to participate.) In 68 day schools the rate among the close contacts was 1.7 per 100 as compared with 0.6 per 100 among the 107 day schools, in which pupils other than close contacts were included. A relatively large incidence of disease among the uninoculated controls occurred in the four mental hospitals in which trials were made. Of a total of 186 controls 21 developed infectious hepatitis, a rate of 11.3 per 100. Most of the patients in these hospitals were older children or adults.

Discussion

In the investigation described here persons exposed to infectious hepatitis were allocated to receive British gammaglobulin or to remain as a control by an effectively random process; the similar inoculated and control groups were then followed up with equal intensity. The local physicians who diagnosed the cases may sometimes have known whether or not the patient had previously received gammaglobulin, but it is not likely that this possibility affected the findings. The great majority of the patients had frank jaundice; moreover, the similarity of the incidence in the inoculated and control groups during the first two weeks, in contrast to the subsequent difference, does not suggest that the diagnosis was biased. Thus the results indicate that in the circumstances of the investigation British gammaglobulin confers a substantial degree of protection against infectious hepatitis.

The findings resemble those obtained with American gammaglobulin, which, in a dose varying with the weight of the subject, has been found to produce substantial protection for periods of at least five to nine months (Stokes *et al.*, 1951; Ward and Krugman, 1962). A feature of the British results is the lack of protection for the first two weeks after inoculation. This lag has also been observed by Stokes *et al.* (1951), and is probably due to the ineffectiveness of gammaglobulin when given during the later stages of the incubation period.

Gammaglobulin, while suppressing the overt features of infectious hepatitis, may not prevent infection and excretion of the causal agent (Ward and Krugman, 1962). Contacts given gammaglobulin should clearly be considered as being potentially infectious.

Gammaglobulin is expensive and there may be a large number of contacts of a single case. Accordingly it would be helpful if the course of an outbreak could be predicted at an early stage. The surveys show that the risk to contacts and hence the necessity for gammaglobulin may vary greatly in different situations, but though the course of each outbreak was analysed its duration and extent could not be reliably foretold at the outset. However, certain main trends were evident. A single case of infectious hepatitis in a day school was the sole case in as many as two-thirds of the schools ; in day schools in which further cases did occur the incidence was usually small. As might be expected the risk among the pupils judged to be in closest contact—for example, those in the same class—was increased. Where gammaglobulin is in short supply its most economical use in day schools would seem to be for the protection of close contacts. Though the number of trials made in institutions other than schools, and also the number of contacts, is small, the findings suggest that the risk to contacts in such locations is considerably greater than in day schools ; note should be taken of the substantial incidence in mental hospitals and children's homes, in which control by other means is especially difficult. Gammaglobulin would seem to be particularly useful in such institutions.

The investigation was not concerned with the efficacy of gammaglobulin among home contacts. The findings do suggest, however, that its practical value would depend on whether it were feasible to give the gammaglobulin either before the home contacts had been infected or at least at an early stage of the incubation period.

Our thanks are due to the Blood Products Laboratory, Lister Institute, for advice about the gammaglobulin and for details of its preparation.

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Infection Risks of Haemodialysis—Some Preventive Aspects

A Report to the Public Health Laboratory Service by the Working Party on Haemodialysis Units*

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Summary : Three aspects of haemodialysis are of special concern to the microbiologist: (1) the hepatitis risk, (2) shunt sepsis, and (3) the hygiene of the equipment used. It is suggested that the risks of infection and cross-infection in haemodialysis units may be diminished by several measures, including the avoidance of overcrowding the patients, setting up codes of practice for the staff, topical disinfection of the patient's skin, and sterilization of equipment. In addition pathologists should emphasize to laboratory staff dealing with specimens from patients that these carry major risks to health.

Introduction

Intermittent haemodialysis for chronic renal failure is now being practised at 28 centres in Britain, and six more main units and two satellite units are in the planning stage. Bacteriologists in several Public Health Laboratory Service (P.H.L.S.) laboratories have been asked for guidance on problems associated with these units, but have found it difficult to obtain reliable information on which to base their advice. A P.H.L.S. working party with power to co-opt experts not in the Service has therefore been set up to study the microbiological aspects of haemodialysis. The working party is anxious to help in tackling some of the practical problems in this field. The following preliminary note on some of the issues that arise may be of use, particularly to laboratory colleagues.

* The working party comprised the following members of the P.H.L.S. staff: Dr. Yvonne E. Cossart, Dr. E. H. Gillespie, Dr. D. M. Jones, Dr. J. C. Kelsey, Dr. B. Moore (chairman and secretary), Dr. I. G. Murray, Dr. Sheila Polakoff, Dr. G. C. Turner, and the following co-opted members: Dr. D. H. D. Burbridge, Dr. J. C. Coleman, Dr. R. M. Stirland.

Reprints may be obtained from Dr. B. Moore at the Public Health Laboratory, Church Lane, Heavitree, Exeter.

Some Technical Aspects

The cellulose film membranes of the artificial kidney separate the two circulations concerned in the dialysis: (1) the patient's blood, which flows from the arterial limb of an arteriovenous shunt inserted into his forearm or leg, through the dialyser, and back into the patient by the venous limb of the shunt ; and (2) the dialysing fluid, prepared from a concentrate and either (*a*) flowing through a Kiil or some type of coil dialyser to waste—that is, "single pass," (*b*) recirculating continuously in a coil for a given period and then being discarded and replaced as in the Travenol machine, or (*c*) flowing continuously through a coil and partially recirculating before being discarded, as in the Baxter Recirculating Single Pass machine.

The dialysing fluid may be prepared in bulk by dilution of a concentrate in a 500-litre plastic tank for single patient treatment or in very much larger tanks for multiple patient treatment. Alternatively, the use of proportioning pumps makes it possible to deliver in a closed system from a concentrate continuously prepared fluid that is controlled by bedside monitors.

The two types of dialyser are the flat-bed Kiil and various forms of presterilized single-use coils. The Kiil has many advantages, in addition to lower running costs. The current model has a blood volume of only up to 140 ml. compared with some of the earlier very large volume coils which required priming with donor blood. The low internal resistance and the small capacity of the blood compartments make a blood pump unnecessary except occasionally where a patient's vascular condition requires it. The Kiil can be used with Cuprophane cellulose membranes, which are thinner and in some respects more effective than the tubular cellophane membranes of coils. The drawbacks of the Kiil are that it takes some time and expertise to rebuild, is more difficult to sterilize, and offers a somewhat greater risk of infection to the operator.